PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2005/007867	International filing date *(day/month/year)* 11.03.2005
Priority date *(day/month/year)* 12.03.2004	
International Patent Classification (IPC) or both national classification and IPC C07C211/52, C07C255/58, C07D207/26, C07D207/08, C07D209/12, C07D295/06, C07D211/60, C07D211/22,	
Applicant LIGAND PHARMACEUTICALS INCORPORATED	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/007867

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/007867

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,3-25,28,29,46-51,58,61-82 (all partially) and 69-77 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 69-77 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1,3-25,28,29,46-51,58,61-82 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1,3-25,28,29,46-51,58,61-82 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US2005/007867

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1,3-25,28,29,46-51 (all partially), 61 (completely), 58,62-82 (all partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,3-25,28,29,46-51,58,61-82
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,3-25,28,29,46-51,58,61-82
Industrial applicability (IA)	Yes:	Claims	1,3-25,28,29,46-51,58,61-68,78-82
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1. Present claim 1 relates to compounds defined by reference to a desirable characteristic or property, namely to "ester, amide or prodrug" of formulae (I)-(VI). The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define compounds by reference to a result to be achieved.

The scope of the claims, with respect to the expression "ester, amide or prodrug thereof", is therefore considered so unclear that a meaningful International Search is impossible with regard to this expression.

III.2. Moreover, the initial phase of the search of the first invention (see point IV: Lack of Unity below) revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible.

Consequently, the search of the first invention has been restricted to compounds of Formula (I) where R1 is NO2 or CN; R2 is hydrogen, an optionally substituted C1-C4 alkyl, or an optionally substituted C1-C4 haloalkyl; R3a is hydrogen or an optionally substituted C1-C4 alkyl; R4, R6, R7, R10 and R11 are each hydrogen, an optionally substituted C1-C6 heterohaloalkyl, an optionally substituted C2-C6 heterohaloalkenyl or an optionally substituted C2-C6 heterohaloalkynyl; R5 is hydrogen or an optionally substituted C1-C4 haloalkyl; R8 is an optionally substituted C1-C4 haloalkyl; and R9 is an optionally substituted C1-C4 haloalkyl (see page 53, lines 7-14).

A complete international preliminary examination of the present application is limited to those parts of the claims for which a complete international search report was established (Rule 66.1(e) PCT). With respect to points III.1. and III.2. above, it should in particular be understood that any positive statement as to novelty and/or inventive step exclusively relates to said limited subject-matter.

III.3. Claims 69-77 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

IV.1. According to Rule 13.1 PCT, "The International application shall relate to one invention only OR to a group of inventions so linked as to form a single general inventive concept".

This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same corresponding special technical features that defines a contribution which each of the claimed inventions, considered as a whole makes over the prior art".

IV.2. The present application relates to compounds according to formulae (I)-(VI) which are androgen receptor modular compounds for the treatment of muscle loss, reduced bone mass, baldness, hirsutism, osteoporosis, hypogonadism, cancer etc... A priori, the only technical feature common to all six general formulae is a phenyl ring substituted by a nitrogen and in para-position to it by a substituent corresponding to the definitions given for R1, R14, or R18.

To decide whether this technical feature is the special technical feature, we must apply the teaching of Rules 13.1 and 13.2 PCT, which stipulate that the technical feature must define a contribution over the prior art to be recognised as the special technical feature (which gives rise to unity).

For the purpose of unity, a single general inventive concept is required. This means that the broadest possible problem to be solved has to be drawn up (i.e. to cover all claimed possibilities). Thus by definition, the provisos may not be taken into account when determining the presence or lack of unity, since the special technical feature must define a contribution over these provisos as well.

It is considered that the problem to be solved by the present application is the provision of further androgen receptor modular compounds for the treatment of muscle loss, reduced bone mass, baldness, hirsutism, osteoporosis, hypogonadism, cancer etc...
The solution is provided by nitrogen-substituted phenyl derivatives according to the formulae (I)-(VI) of claim 1.
Thus, the single general concept can be identified as the provision nitrogen-substituted phenyl derivatives according to the formulae (I)-(VI) of claim 1 as androgen receptor modular compounds for the treatment of muscle loss, reduced bone mass, baldness, hirsutism.

IV.3. The following documents D1-D4 were retrieved during the preliminary search:

D1: DATABASE WPI Section Ch, Week 200424 Derwent Publications Ltd., London, GB; Class B02, AN 2004-257164 XP002331455 -& WO 2004/016576 A1 (TAKEDA CHEM IND LTD) 26 February 2004 (2004-02-26)

D2: EP-A-1 122 242 (YAMANOUCHI PHARMACEUTICAL CO. LTD) 8 August 2001 (2001-08-08)

D3: US-A-4 097 578 (PERRONNET ET AL) 27 June 1978 (1978-06-27)

D4: WO 03/011824 A (BRISTOL-MYERS SQUIBB COMPANY; SUN,

CHONGQING; ROBL, JEFFREY, A; SALVAT) 13 February 2003 (2003-02-13)

D1 discloses androgen receptor modulators for the treatment of hypogonadism, osteoporosis, cancer, consisting of a naphthalene ring substituted by N-pyrrolidinyl and p-CN. Compound number 155 on page 230 actually falls within the scope of formula (IV) of present claim 1.

D2 and D3 relate to androgen receptor antagonists for the treatment of cancer, hirsutism, baldness, comprising a p-nitrophenyl derivatives substituted by a cyclic nitrogen (see in D2: page 39: compound 1-33; page 1; claims 7 and 9 and in D3: column 1 and 2).

D4 also describes androgen receptor modulators which are nitro-naphthalene rings substituted by a cyclic nitrogen in para position (see example 1 and claims 7-11).

Thus, in view of the teaching of the prior art documents D1-D4, the use phenyl rings substituted by a nitrogen and in para-position by a substituent R1, R14, or R18 as androgen receptor modular compounds for the treatment of muscle loss, reduced bone mass, baldness, hirsutism, osteoporosis, hypogonadism, cancer cannot be considered as inventive and the above mentioned technical feature cannot be regarded as a special technical feature, since it does not make up the contribution over the prior art. Therefore, the single general concept which could link the different inventions of the present application cannot be considered as inventive and there is a lack of unity.

IV.4. In the light of the above, the examiner has identified 6 different subjects:

1.) Compounds of general formula (I) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82.

2.) Compounds of general formula (II) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82.

3.) Compounds of general formula (III) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82.

4.) Compounds of general formula (IV) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82.

5.) Compounds of general formula (V) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82.

6.) Compounds of general formula (VI) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82.

IV.5. Since the International Search Report has been established for those parts of the claims relating to the first invention, the following examination is therefore limited to the subject-matter of the first invention. In this context, take also note of the restricted search and the non-establishment of opinion mentioned under point III above.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D6: ANLEZARK G M ET AL: "BIOACTIVATION OF DINITROBENZAMIDE MUSTARDS BY AN E.COLI B NITROREDUCTASE" BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB, vol. 50, no. 5, January 1995 (1995-01), pages 609-618, XP000645552 ISSN: 0006-2952

D7: PANTHANANICKAL, AUGUSTINE ET AL: "Structure-activity relationship of aniline mustards acting against B-16 melanoma in mice" JOURNAL OF MEDICINAL CHEMISTRY , 22(10), 1267-9 CODEN: JMCMAR; ISSN: 0022-2623, 1979, XP002331449

D8: GRAVATT, G. LANCE ET AL: "DNA-Directed Alkylating Agents. 6. Synthesis and Antitumor Activity of DNA Minor Groove-Targeted Aniline Mustard Analogs of Pibenzimol (Hoechst 33258)" JOURNAL OF MEDICINAL CHEMISTRY , 37(25), 4338-45 CODEN: JMCMAR; ISSN: 0022-2623, 1994, XP002331450

D9: TURNBULL, KENNETH ET AL: "The reaction of 4-substituted aryl isocyanates

with NaBH4/trifluoroacetic acid (TFA)" SYNTHESIS , (3), 391-392 CODEN: SYNTBF; ISSN: 0039-7881, 1999, XP008048153

D10: NICULESCU-DUVAZ D ET AL: "Self-immolative nitrogen mustard prodrugs for suicide gene therapy" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 26, 17 December 1998 (1998-12-17), pages 5297-5309, XP002265049 ISSN: 0022-2623

D11: EP-A-0 711 768 (MITSUI TOATSU CHEMICALS, INC; MITSUI CHEMICALS, INC) 15 May 1996 (1996-05-15)

D12: PALMER, BRIAN D. ET AL: "Hypoxia-selective antitumor agents. 5. Synthesis of water-soluble nitroaniline mustards with selective cytotoxicity for hypoxic mammalian cells" JOURNAL OF MEDICINAL CHEMISTRY , 35(17), 3214-22 CODEN: JMCMAR; ISSN: 0022-2623, 1992, XP002331451

D13: PALMER, B. D. ET AL: "Nitro analogs of chlorambucil as potential hypoxia-selective anti-tumor drugs" ANTI-CANCER DRUG DESIGN , 5(4), 337-49 CODEN: ACDDEA; ISSN: 0266-9536, 1990, XP008048139

D14: PALMER, BRIAN D. ET AL: "Hypoxia-selective antitumor agents. 3. Relationships between structure and cytotoxicity against cultured tumor cells for substituted N,N-bis(2-chloroethyl)anilines" JOURNAL OF MEDICINAL CHEMISTRY , 33(1), 112-21 CODEN: JMCMAR; ISSN: 0022-2623, 1990, XP000609118

D15: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PRASMICKIENE, G. ET AL: "Synthesis and study of the reactivity of p-[bis(2- chloropropyl)amino]phenylalkanoic acids" XP002331454 retrieved from STN Database accession no. 1969:430178

D16: POPP, FRANK D.: "Synthesis of potential anticancer agents. X. Preparation and reactions of aldehydes related to benzaldehyde mustard" JOURNAL OF MEDICINAL CHEMISTRY , 7(2), 210-12 CODEN: JMCMAR; ISSN: 0022-2623, 1964, XP002331453

D17: STEINMAN, MARTIN ET AL: "1-Poly(fluoroalkyl)benzodiazepines" JOURNAL OF MEDICINAL CHEMISTRY , 16(12), 1354-60 CODEN: JMCMAR; ISSN: 0022-2623, 1973, XP002295070

D18: ABELA MEDICI, ANTHONY J. ET AL: "Cytotoxic compounds. Part 21.

Chloro-, methoxy-, and methoxycarbonyl-derivatives of (bis-2-chloroethylamino)-phenols and anilines" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1: ORGANIC AND BIO-ORGANIC CHEMISTRY (1972-1999) , (20), 2258-63 CODEN: JCPRB4; ISSN: 0300-922X, 1977, XP008048335

D19: US-A-4 202 895 (INABA, SHIGEHO ET AL) 13 May 1980 (1980-05-13)

D20: WO 02/16310 A (GTX, INC; DALTON, JAMES; MILLER, DUANE, D; YIN, DONGHUA; HE, YALI) 28 February 2002 (2002-02-28)

D21: WO 98/22432 A (YAMANOUCHI PHARMACEUTICAL CO., LTD; TANIGUCHI, NOBUAKI; OKADA, MINORU;) 28 May 1998 (1998-05-28)

V.1. Novelty:

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,3-25,28,29,46-51,58,61-82 is not new in the sense of Article 33(2) PCT:

Documents D6, D7, D12, D14, D16, and D18 disclose compounds for the treatment of cancer or tumours falling within the scope of the general formula (I) of present claim 1 (see International Search Report for details on relevant passages).

Documents D8, D9, D10, D11, D13, D15, D17, D19 discloses further compounds falling within the scope of the present formula (I) (see International Search Report for details).

Consequently, the subject-matter of claims 1,3-25,28,29,46-51,58,61-82 is not novel over the prior art (Article 33(29 PCT).

V.2. Inventive Step:

Since the subject-matter of claims 1,3-25,28,29,46-51,58,61-82 is not novel, it cannot considered as involving an inventive step either (Article 33(3) PCT).

V.3. Industrial Applicability:

The present application relates to compounds which are useful for the treatment of muscle loss, reduced bone mass, baldness, osteoporosis, cancer and the subject-matter of claims 1,3-25,28,29,46-51,58,61-68,78-82 is therefore considered as industrially applicable (Article 33(4) PCT).

For the assessment of the present claims 69-77 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.